REMARKS

Entry of the above amendments to the specification and claims is respectfully requested.

Claims 1-9 were originally filed. Claims 10-15 were added in the Preliminary Amendment filed April 8, 2003. Claim 8 is cancelled herein and Claims 16-22 are added herein.

Restriction Requirement:

The Examiner has required restriction of the claimed subject matter under 35 U.S.C. § 121 to one of the following inventions:

I. Claims 1-13, drawn to compositions of GM-CSF and methods of using such to treat inflammatory bowel disease, classified in class 424, subclass 198.1.

II. Claims 14 and 15, drawn to treatment of ulcers, classified in class 424, subclass 198.1.

Applicants hereby affirm the election of Group I without traverse. Claims 14 and 15 stand withdrawn from further consideration by the Examiner as being directed to non-elected subject matter. Applicants reserve the right to file separate divisional applications on the non-elected subject matter of these claims at a later date.

Formal Matters:

The Examiner contends that the title of the invention is not descriptive. In particular, the Examiner contends that the title should convey that EDTA is the stabilizing agent of the invention.

Applicants respectfully disagree with the Examiner's contention. EDTA is only one of the various chelating agents suggested for use in the invention in the specification (see page 3, lines 6-20). However, in the interest of conforming the Title of the Invention to the claimed subject matter, the Title of the Invention has been replaced with the following::

"STABILIZED FORMULATIONS OF GRANULOCYTE MACROPHAGE COLONY-STIMULATING FACTOR"

This title is more descriptive than the original title in that the invention is actually directed to both aqueous and lyophilized formulations of granulocyte macrophage colony-stimulating factor (GM-CSF).

The Examiner also objected to Claim 8 under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. In particular, the Examiner contends that the further step of lyophilizing the aqueous solution, as recited in claim 8, would not produce a stabilized aqueous solution, as recited in claim 5.

Applicants have cancelled Claim 8 and have added new Claims 16-22 in place thereof. In particular, new Claims 16-18 are directed to a lyophilized formulation of recombinant GM-CSF, and new Claims 20-22 are directed to a process of preparing such formulations. These new claims are fully supported in the specification as originally filed (see pages 4-5 of the specification) and therefore do not add any new matter to the specification.

Rejection of Claims 9-15 under 35 U.S.C. §112, ¶2:

The Examiner has rejected Claims 9-15 under 35 U.S.C. §112, ¶2, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner contends that Claims 9, 10 and 14 are incomplete methods claim, as they do not require any significant amount of GM-CSF. Claims 11-13 and 15 are rejected for depending from an indefinite claim.

As suggested by the Examiner, Applicants have amended Claims 9, 10 and 14 to insert the phrase "a therapeutically effective amount of" before the words "an aqueous" in Claim 9, and before the words "the aqueous" in Claims 10 and 14, thereby overcoming this rejection of Claims 9-15 under 35 U.S.C. §112, ¶2.

Rejection of Claims 1-9 under 35 U.S.C. §103(a):

The Examiner has rejected Claims 1-9 under 35 U.S.C. §103(a) as being unpatentable over the LEUKINE® Sargramostim product insert, cited by Applicants in paper number 5, in view of Chalmers, Manufacturing Chemist & Aerosol News (March 1978, cited by Applicants), and U.S. Patent Number 5,217,954 (Foster et al.), and in the case of claims 4-8, further in view of U.S. Patent Number 5,545,536 (Kaushansky et al.).

In particular, the Examiner contends that:

The Leukine® patient insert teaches that sargramostim is provided in liquid form at a concentration of 500 mcg/mL (micrograms per milliliter), with 1.1% benzyl alcohol, 40 mg/mL mannitol, 10 mg/mL sucrose, and 1.2 mg/mL tromethamine (third paragraph of insert). At the bottom of the first column of the third page, and again on the fifth page, there are warnings that preparations containing benzyl alcohol, including both LEUKINE® liquid and lyophilized LEUKINE® reconstituted for injection, should not be used in neonates. The LEUKINE® (sargramostim) insert differs from the claims in that it does not teach inclusion of EDTA, nor the inclusion of TRIS-HCL.

Chalmers teaches the use of EDTA as a chelating agent in foods, toiletries and medicines. He states that "The EDTA range of chelating agents is designed to enable as many different kinds of metals as possible to be controlled or de-ionised as a complex molecule in aqueous solution (page 79). At page 80, he teaches that although EDTA has no germicidal action per se, it will inhibit the growth of certain bacteria by rendering unavailable trace metals required for growth.

Foster et al. teach the use of EDTA as a chelating agent for the stabilization of bFGF, another cytokine. At column 1, they state that the EDTA "stabilizes this protein against oxidation of its free cysteine residues or metal-induced aggregation, thereby preserving the homogeneity of the purified product."

The use of TRIS as a buffering agent in protein and pharmaceutical preparations is notoriously old and well known in the art. For example, Kaushansky et al. teach the use of TRIS buffers in the isolation of GM-CSF, see for example column 17.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to have substituted EDTA for benzyl alcohol in the preparations of sargramostim disclosed in the LEUKINE® insert. One of ordinary skill in the art would have been motivated to make the substitution in order to produce a stable composition that could be administered to neonates, as the insert specifically warns against administering benzyl alcohol to neonates. The specific concentration of EDTA to be added would be easily determinable, and is considered well within the purview of routine experimentation by the ordinary pharmacologist. It further would have been obvious to use TRIS as a buffering agent, as it is notoriously old and well known in the art as such, for example see Kaushansky. Accordingly, the invention, taken as a whole, is *prima facie* obvious over the prior art.

The Examiner notes the results disclosed at page 13 of the specification. The results therein are not considered to be "unexpected", as the person of ordinary skill in the art reading the above-cited references would have expected GM-CSF stored in the presence of EDTA to be more stable than that without. It would appear that the results therein merely compare the presence to the absence of EDTA, and do not compare the preparations containing EDTA to comparable prior-art preparations lacking EDTA.

Applicants respectfully traverse this rejection for the following reasons.

The present invention came about by the surprising observation that GM-CSF (specifically LEUKINE® Sargramostim) partially degraded at its N-terminus when stored as a formulation in ready-to-inject syringes over long periods of time. The resulting truncated species of GM-CSF retained high levels of bioactivity but there was concern that such species may possess undesirable alterations in their *in vivo* pharmologic properties. Thus, the problem that was solved by the invention was the production of formulations of GM-CSF that could be stored in ready-to-inject syringes over long periods of time without degradation of the N-terminus of the GM-CSF. This solution came about by the adding a chelating agent, such as EDTA, to the formulation.

The Examiner, in making her conclusion that this solution is obvious in view of these references, appears to be of the belief that the problem solved by the instant invention is the replacement of the benzyl alcohol of the formulation disclosed in the product insert with EDTA in order to provide stable formulations for use in newborns. As stated above, such is not the case. Benzyl alcohol is generally used as a bacteriocide for products requiring the presence of water. EDTA, as noted by Chalmers, can also be used as a bacterocide due to its ability to remove trace metals required for bacterial growth. The Examiner contends that one of ordinary skill in the art would be motivated by the teachings of Chalmers to replace the benzyl alcohol in the formulations disclosed in the product insert with EDTA in order to produce a stable formulation for use in neonates. This contention might have some merit if it were not for the statement in the specification that benzyl alcohol can also be added to the claimed formulations as a perservative (see page 3, line 27). Accordingly, the teachings of Chalmers would not motivate one of ordinary skill in the art to add EDTA to the formulation disclosed in the product insert in order to prevent the GM-CSF from degrading at its N-terminus without some additional teaching to do so.

Foster does not provide this additional teaching. Foster teaches the use of a chelating agent, such as EDTA, in bFGF formulations in order to prevent the oxidation of bFGF's free cysteine residues or the formation of multimers of bFGF by metal-induced aggregation. The problem solved by the teachings of Foster is obviously not the same as the

problem solved by the present invention. As noted above, the problem solved by the present invention is the prevention of the clipping of the full-length GM-CSF molecule at its *N*-terminus. This clipping, which results in the formation of truncated forms of GM-CSF, was previously unknown for GM-CSF formulations. Furthermore, the possibility that this clipping was due to a metal ion catalyzed process was also unknown prior to the present invention. Thus, one of ordinary skill in the art, armed with the knowledge of the teachings of Foster wherein EDTA is used to stabilize bFGF formulations in order to prevent oxidation or metal-induced aggregation, fwould not be motivated to add EDTA to the formulation of the product insert in order to prevent the degradation of the GM-CSF at its N-terminus without some additional teaching.

Kaushansky does not provide this additional teaching either, nor does Kaushansky disclose or suggest the need to add chelating agents to the purified GM-CSF compositions disclosed therein.

It is apparent from the foregoing remarks that the additional teaching required to provide the necessary motivation for one of ordinary skill in the art to add a chelating agent to the formulation disclosed in the product insert in order to prevent the degradation of the GM-CSF contained therein must come from Applicants' own teachings in the specification. This is particularly apparent when one considers that none of the cited references disclose or suggest the addition of a chelating agent to a GM-CSF formulation in order to prevent the GM-CSF from degrading at its N-terminus, nor do any of the cited references provide the necessary motivation for one of ordinary skill in the art to make such an addition. Using the Applicants' own teachings in the specfication to reject the invention as being unpatentable in light of the cited references is a rejection based on hindsight, and, as such, is clearly impermissible.

Consequently, for the reasons set forth above, Applicants respectfully submit that Claims 1-9 are not obvious in view of the teachings of the LEUKINE® Sargramostim product insert, Chalmers, Foster, and Kaushansky, either taken alone or in combination. Accordingly, Applicants respectfully request that the rejection of these claims under 35 U.S.C. §103(a) be withdrawn and that these claims be allowed to issue forthwith.

Rejection of Claims 10-13 under 35 U.S.C. §103(a):

The Examiner has rejected Claims 10-13 under 35 U.S.C. §103(a) as being unpatentable over the LEUKINE® Sargramostim product insert, Chalmers, Foster, and further in view of U.S. Patent Number 6,500,418 B1 (Dieckgraefe et al.).

In particular, the Examiner contends that:

> **Claims 10-13 are drawn to methods of treating IBD, including Crohn's disease, using the composition of claim 1. The references cited in the rejection of claims 1-9 do not specifically disclose treatment of IBD/Crohn's disease with GM-CSF. Dieckgraefe et al. disclose and claim treatment of Crohn's disease with GM-CSF, see claims 1 and 21, especially. It therefore would have been obvious to the person of ordinary skill in the art to substitute the composition of claim 1 in the method of Dieckgraefe et al. to attain the known and expected benefits of treating Crohn's disease with GM-CSF, as disclosed by Dieckgraefe et al.**

Applicants respectfully traverse this rejection for the following reasons:

As noted above, the composition of Claim 1 is not obvious in view of the combined teachings of LEUKINE® Sargramostim product insert, Chalmers, and Foster due to the fact that none of the teachings of the references provide the necessary motivation for one skilled in the art to add a chelating agent to a formulation of GM-CSF in order to prevent the GM-CSF from degrading at its N-terminus when the formulation is stored for a period of time. The teachings of Dieckgraefe also fail to provide the necessary motivation required for one of ordinary skill in the art to add the chelating agent. Thus, the composition of Claim 1 is additionally not obvious in light of the teachings of Dieckgraefe. Consequently, Applicants respectfully submit that the methods of using the composition of Claim 1, as set forth in Claims 10-13 would also not be considered obvious in light of the teachings of Dieckgraefe. Accordingly, Applicants respectfully request that the rejection of Claim 10-13 in view of Dieckgraefe under 35 U.S.C. §103(a) be withdrawn and that these Claims be allowed to issue forthwith.

Conclusion:

In view of the foregoing amendments to the claims and Remarks, Applicants respectfully submit that all of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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